



Spray dried cubosomes as effective vaccine delivery system

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Aim

The aim of this study was to spray dry cubosomes with ovalbumin (OVA) as model antigen and Quil-A as adjuvant and investigate *in vitro* characteristics and *in vivo* immunogenicity following subcutaneous (s.c.) and oral administration to mice. Since oral vaccination with cubosomes had no effect, we applied microcontainers (MC) as oral delivery system, characterized the system *in vitro* and evaluated its oral immunogenicity *in vivo* as oral booster following s.c. injected primer and in an oral prime-boost setting.

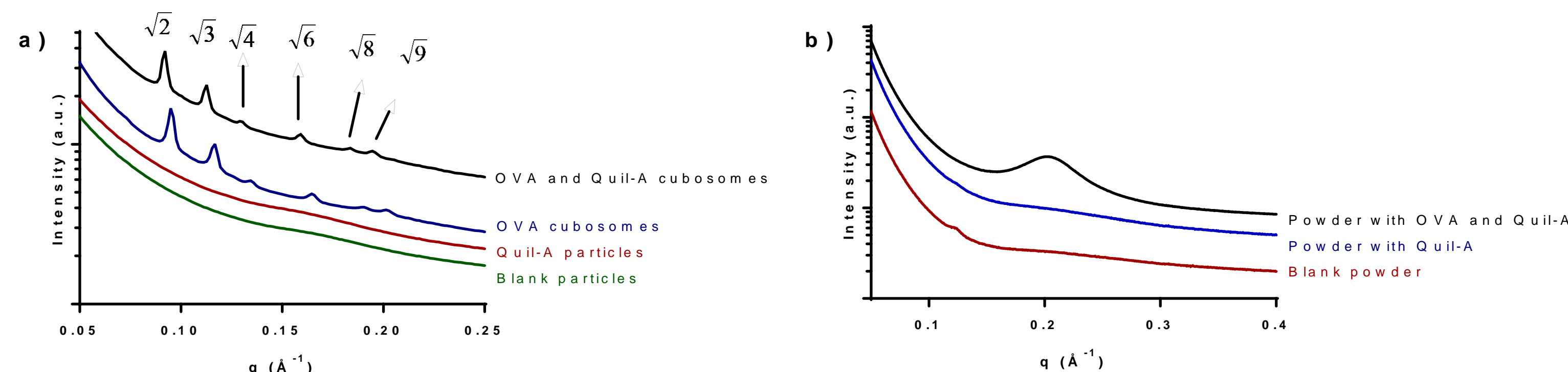
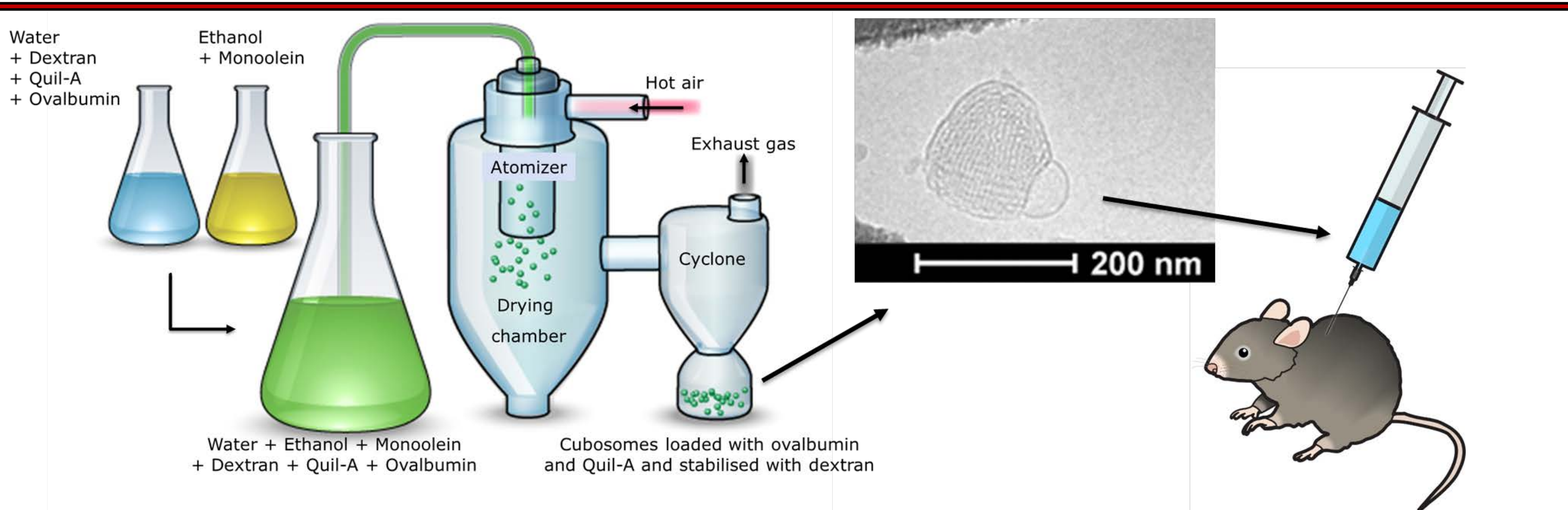


Figure 1: q vs intensity patterns obtained from SAXS measurements of a) dispersions in water of cubosomes with no Quil-A or OVA (blank), only Quil-A, only OVA, and OVA and Quil-A. b) Spray dried powders of monoolein and dextran with no Quil-A or OVA (blank), only Quil-A, and with OVA and Quil-A.

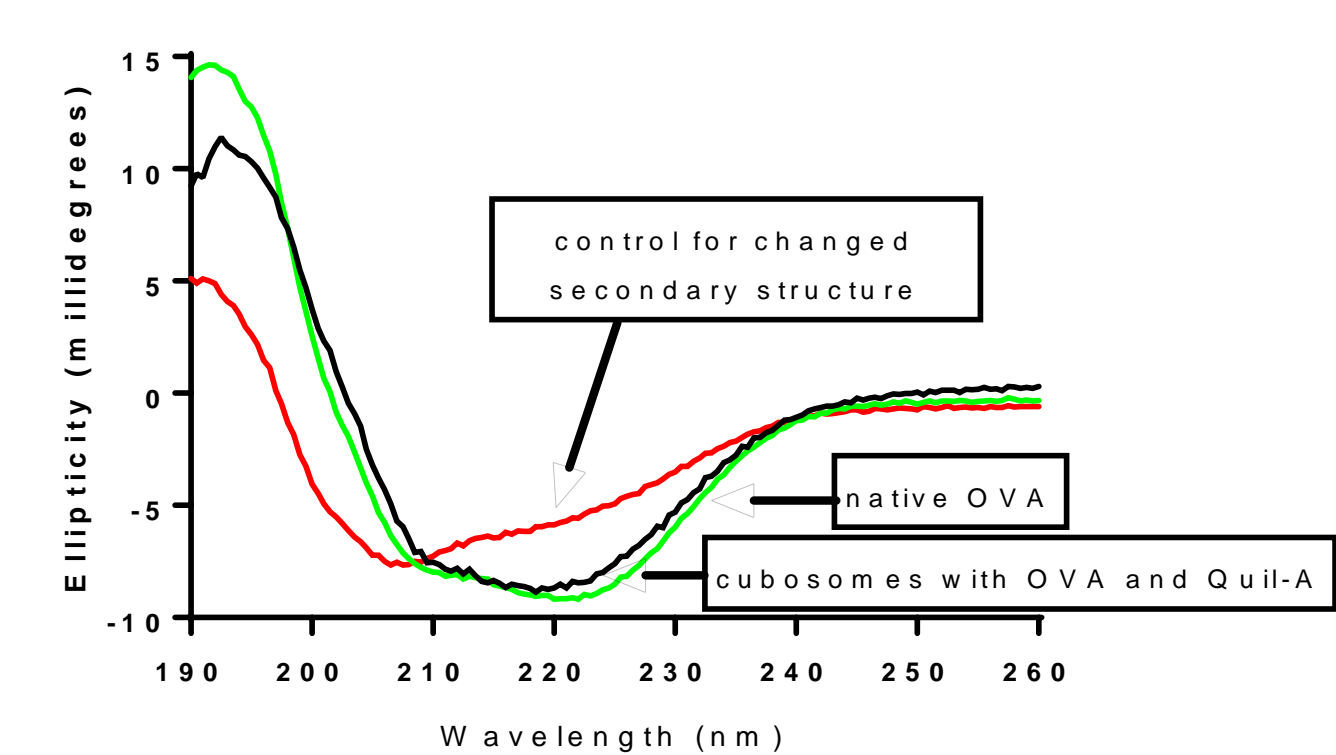


Figure 2: Representative circular dichroism spectra of spray dried cubosomes with OVA and Quil-A after secondary drying at 86°C for 24 h (concentration of OVA was 106 µg/mL).

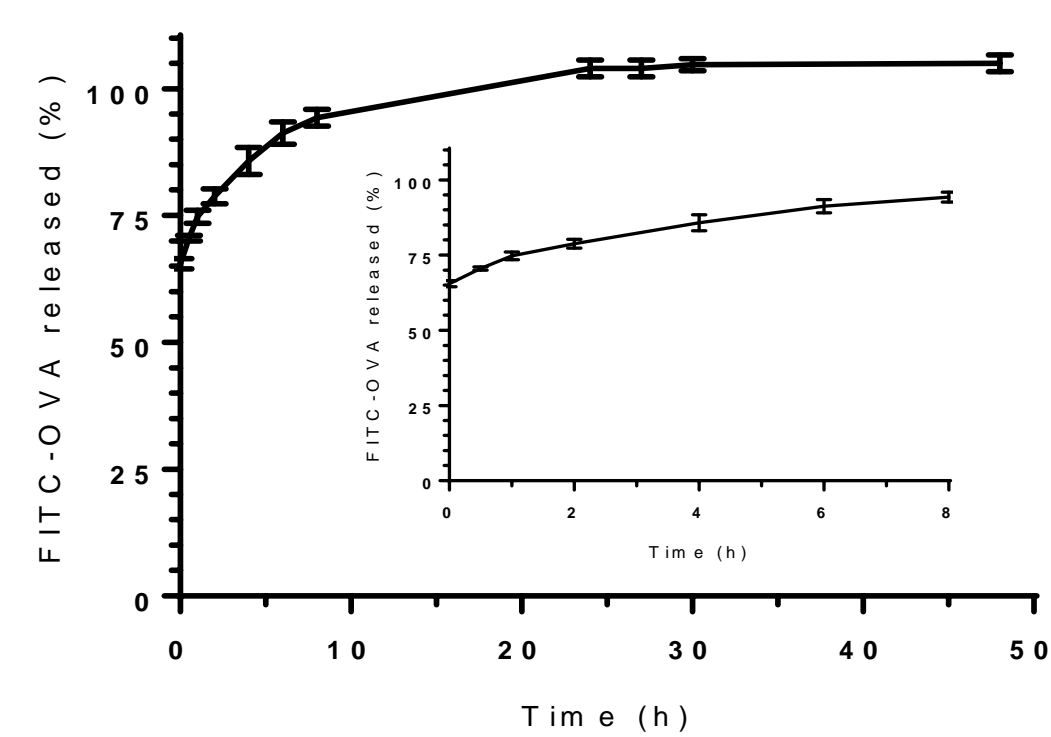


Figure 3: Release of FITC-OVA from cubosomes (also containing Quil-A) in 9.5 mM PBS at pH 7.3 and 37°C. The insert shows the release over the first 8 h. Data are expressed mean ± SD (n = 4).

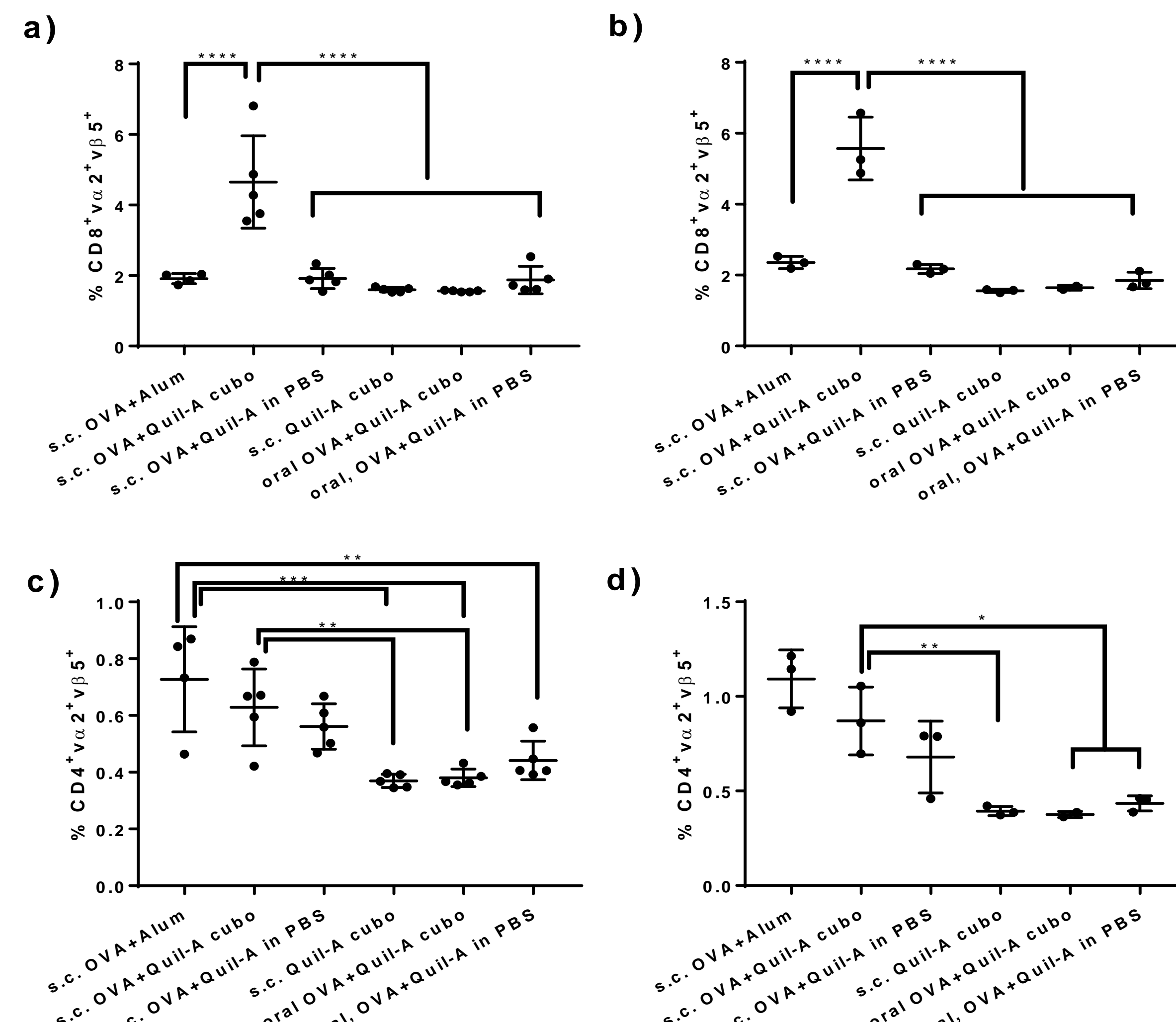


Figure 4: *In vivo* expansion of transgenic CD8⁺ cells (a and b) and CD4⁺ cells (c and d) in spleens (a and c) and lymph nodes (b and d) following s.c. or oral administration. Data in a and c are results from individual mice plus the mean and SD from a representative experiment of three independent experiments (n = 5 mice/experiment). Data in b and d are pooled data from 4-5 mice in each of three independent experiments. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

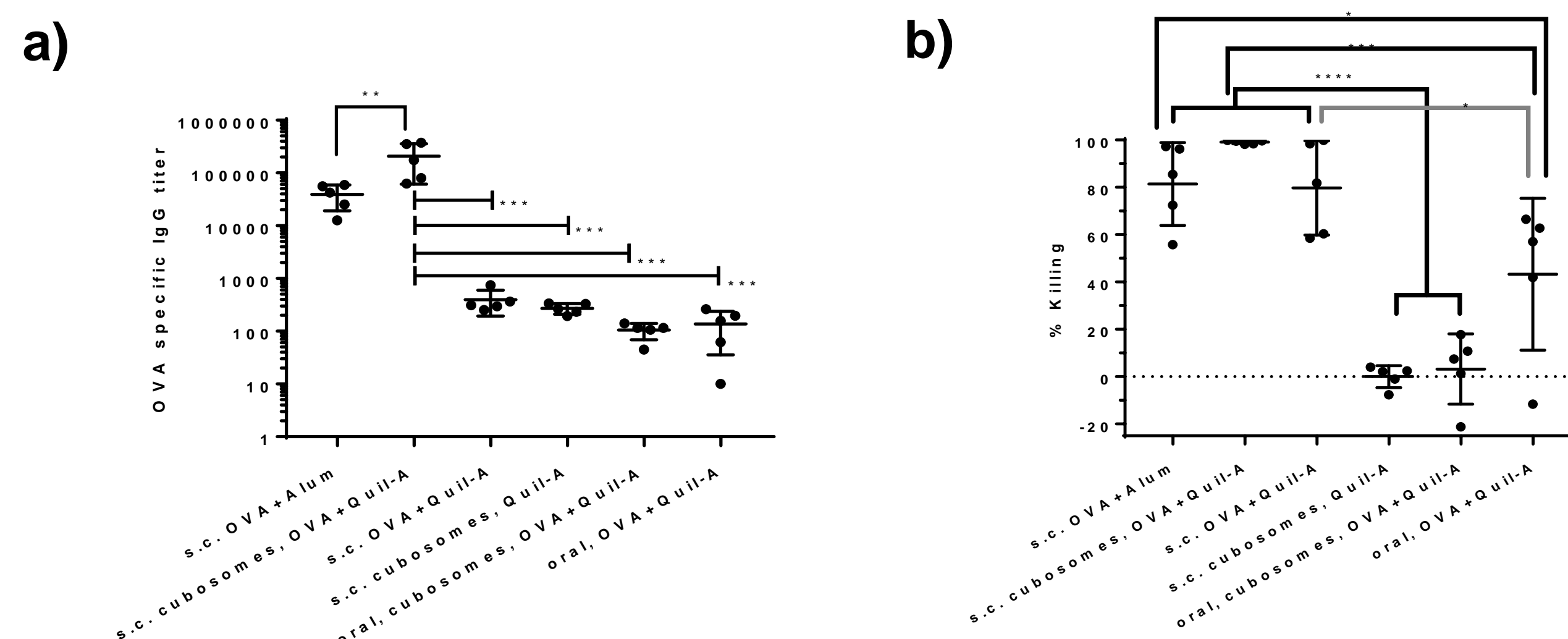


Figure 5: OVA specific serum IgG antibody titers (a) and target cell killing in spleens (b). Data shown are from individual mice from a representative experiment of 3 independent experiments (n = 5 mice/experiment). **p < 0.01, ***p < 0.001, ****p < 0.0001

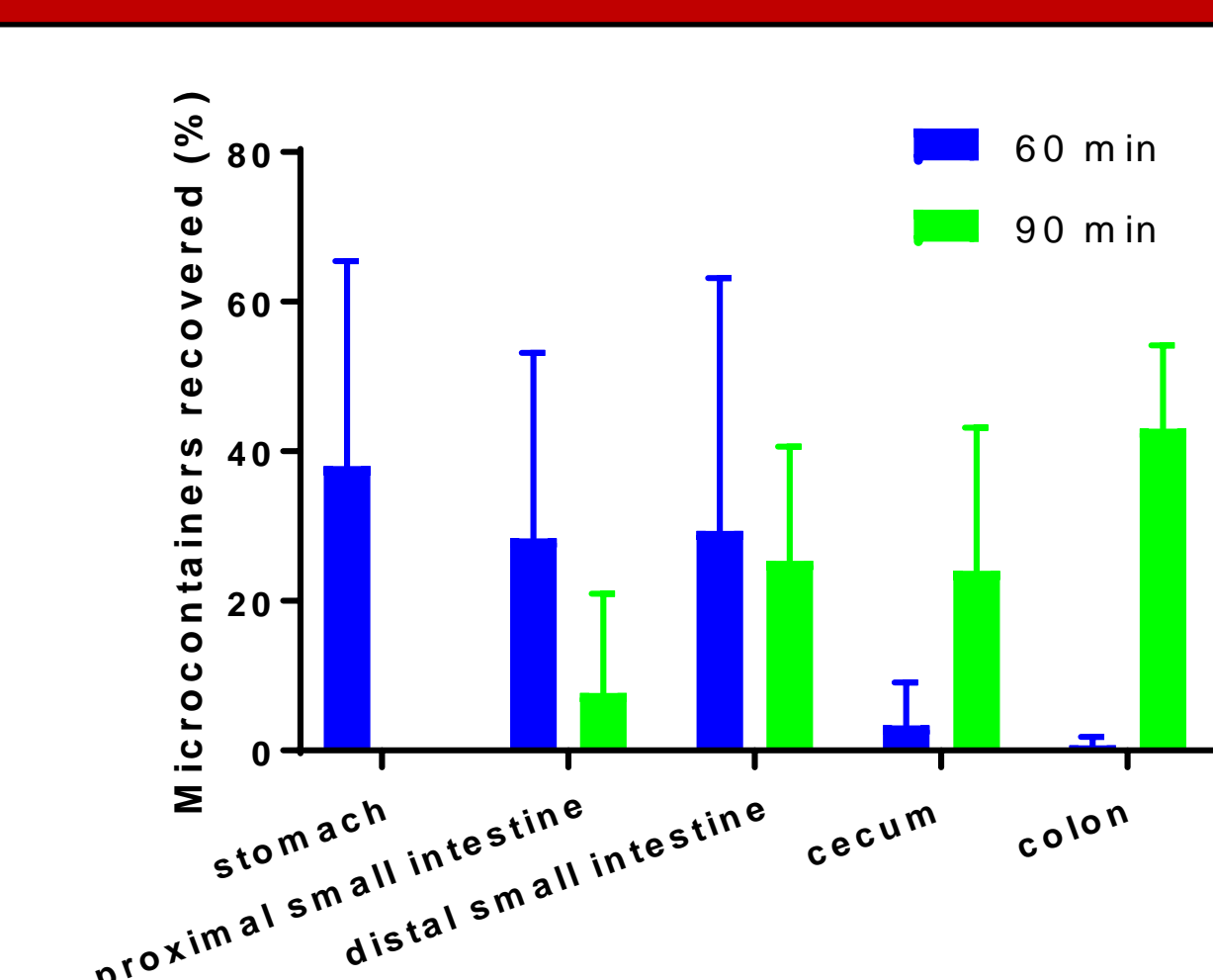
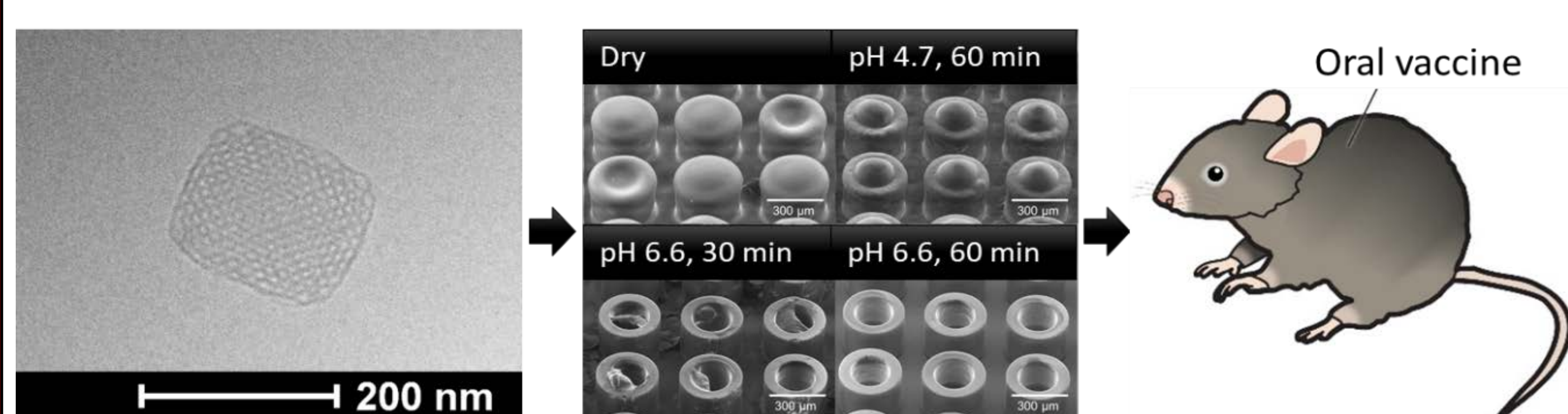


Figure 6: Microcontainers found in segments of the GI tract when sacrificing mice 60 or 90 min after oral gavage. Data are presented as mean±SD (n = 3).

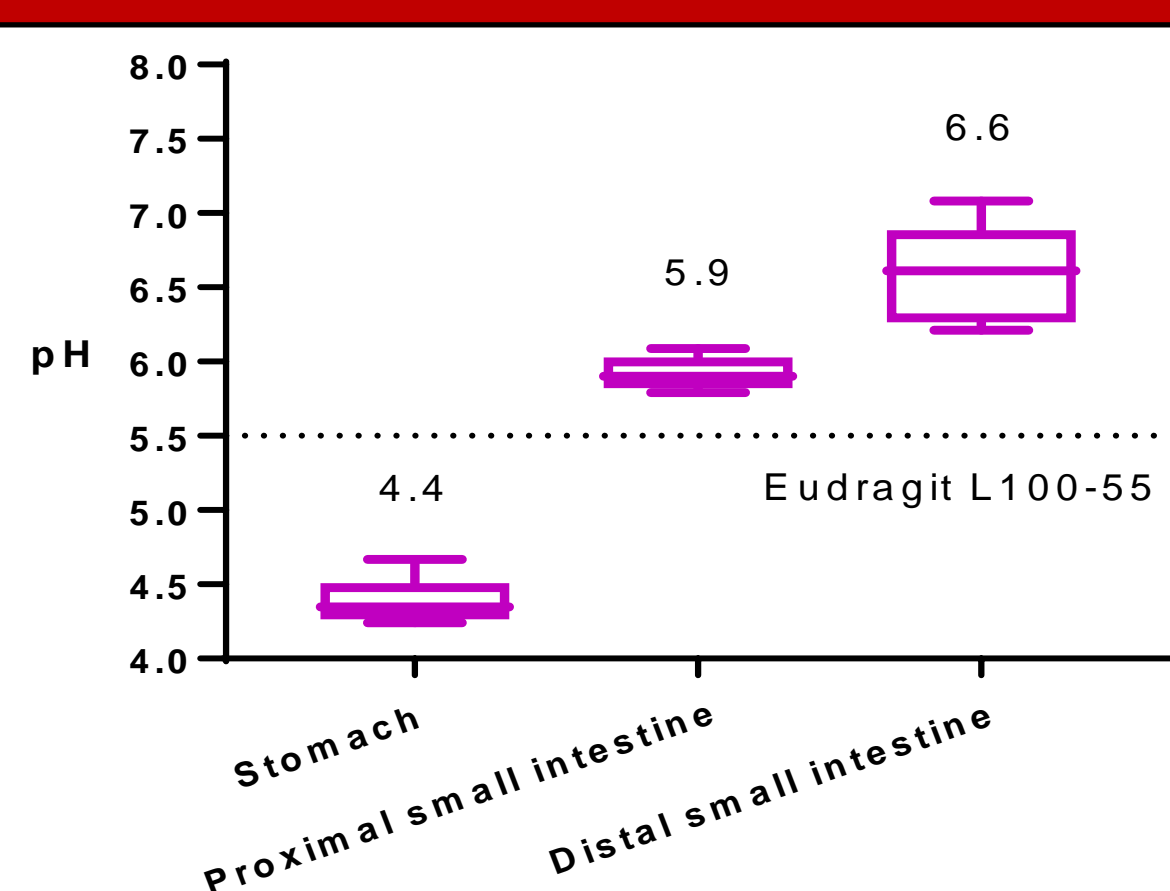


Figure 7: pH in the GI tract of mice at 37°C. Whiskers on the boxplots indicate maximum and minimum (n = 5). Averages are written above each group.

Conclusions

Cubosomes with OVA and Quil-A stimulate strong humoral and cellular immune responses after s.c. administration but not oral. MC protect cubosomes *in vitro* and release them in the small intestine. MCs improve immunogenicity *in vivo* of oral boosters but no effect is seen after oral primer and booster.

Acknowledgements

This work was supported by the Danish National Research Foundation (DNRF122) and Villum Fonden (Grant No. 9301) for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN).

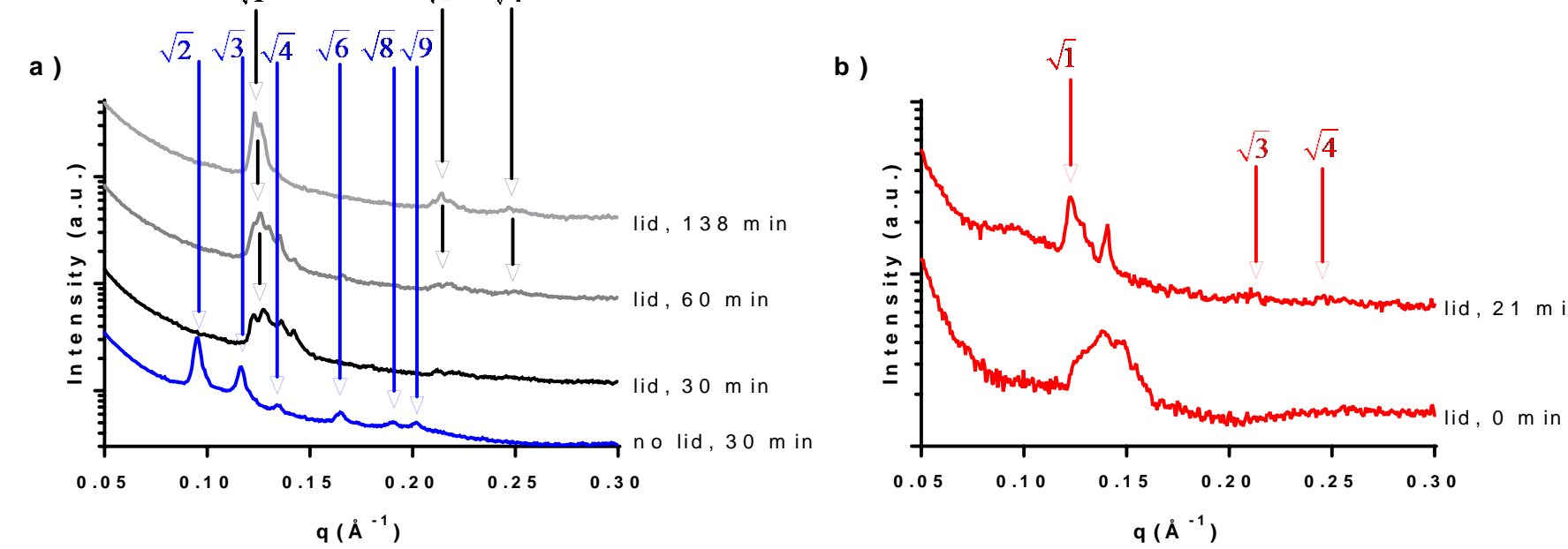


Figure 8: q vs. intensity patterns obtained from SAXS measurements of cubosomes with OVA and Quil-A released at 37°C from microcontainers with or without Eudragit L100-55 lids as indicated in PBS (a) and mouse intestinal medium (b).

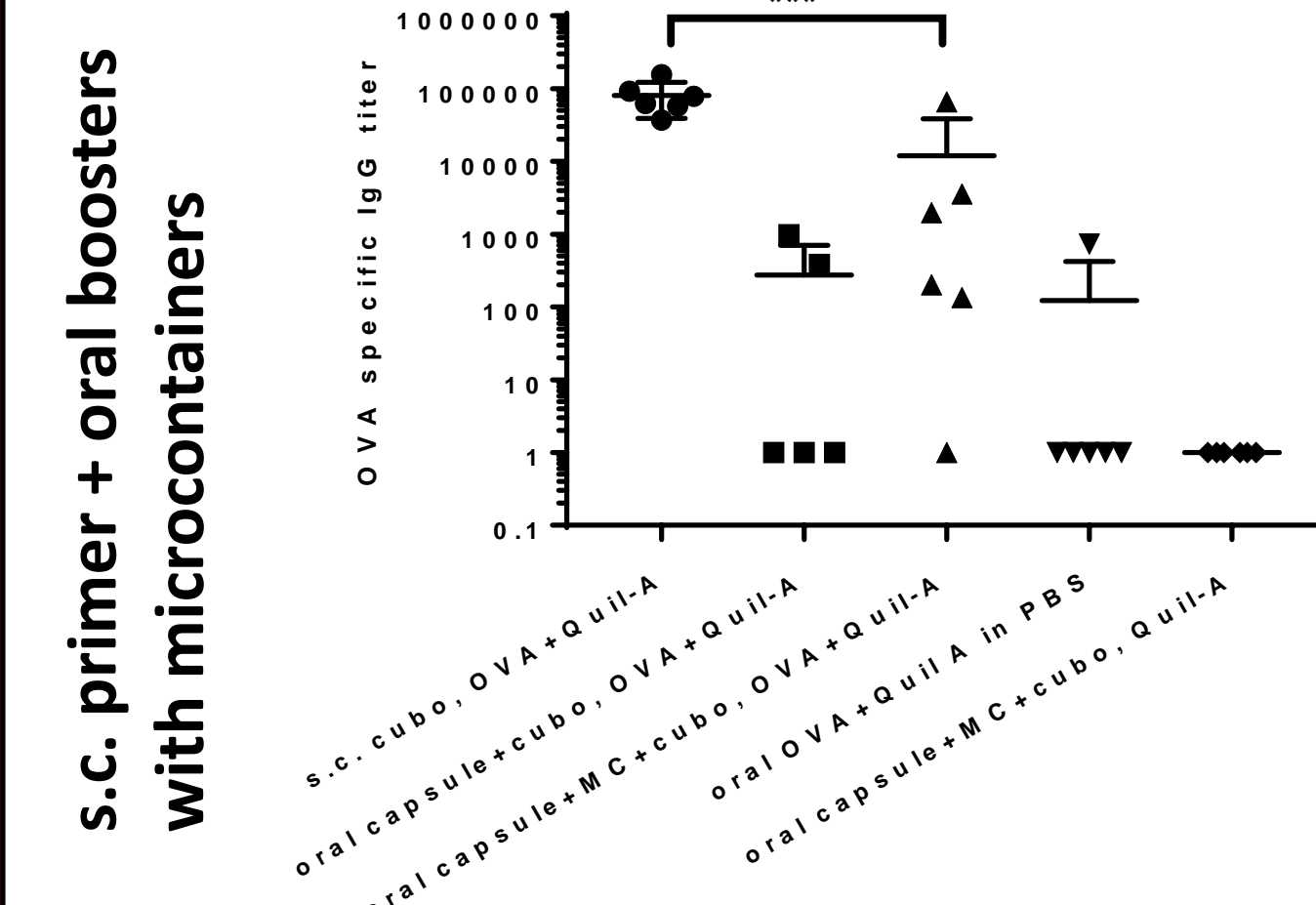


Figure 9: OVA specific serum IgG antibody titers from individual mice from a representative experiment of 3 independent experiments (n = 5 mice/experiment). ***p < 0.001

Oral primer and boosters with microcontainers

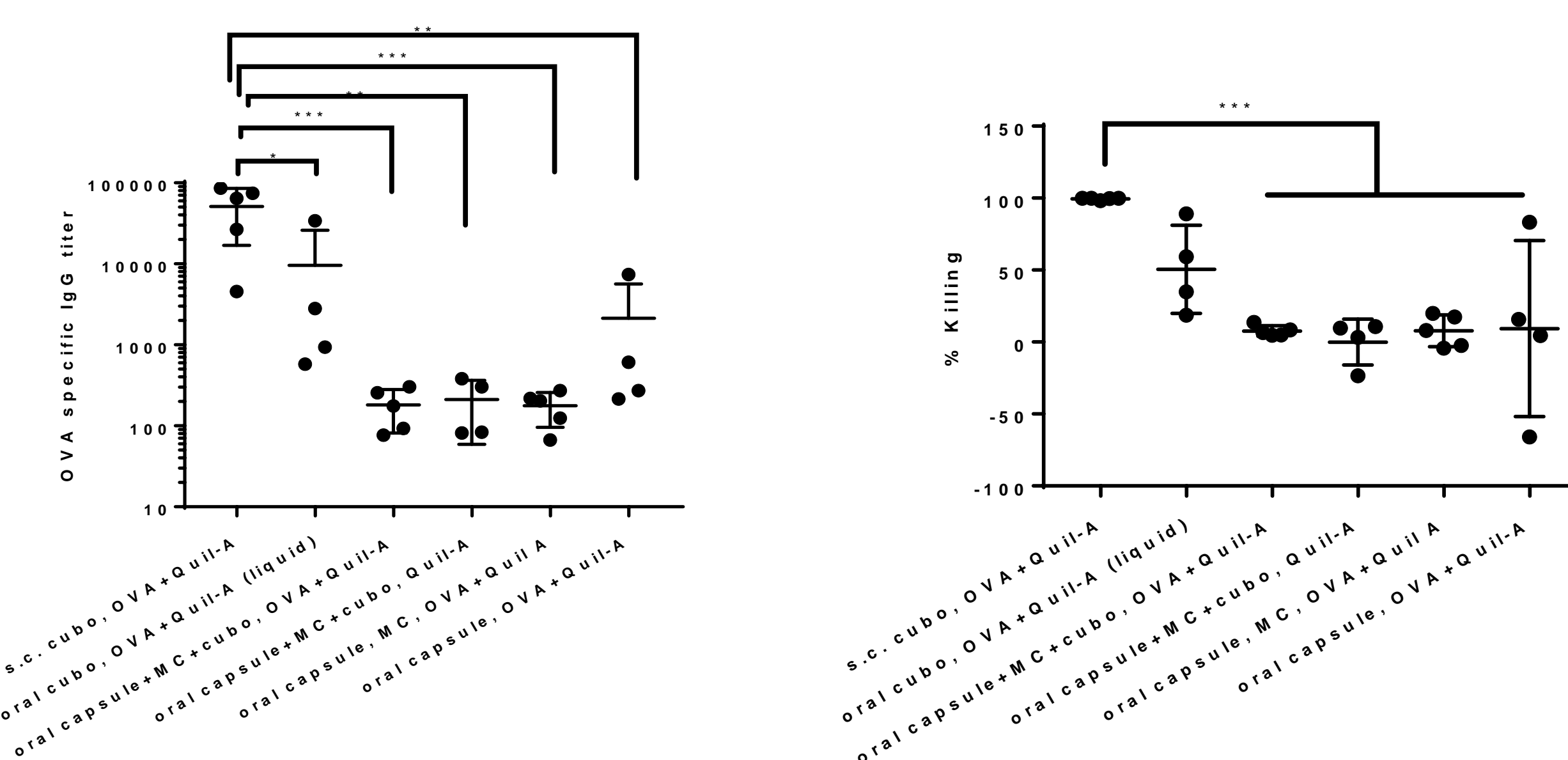


Figure 10: OVA specific serum IgG antibody titers (a) and target cell killing in spleens (b). Data shown are from individual mice from a representative experiment of 2 independent experiments (n = 5 mice/experiment). *p < 0.05, **p < 0.01, ***p < 0.001

